Ph.D. Thesis Summary

PD-CATALYSED CROSS-COUPLING OF FLUOROUS ORGANOSILANES

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1. INTRODUCTION

Liquid perfluoroalkanes (C_nF_{2n+2}, *fluorocarbons*) have unique properties. They are simultaneously hydrophobic and lipophobic, highly apolar, chemically inert and non-toxic; their molecules have extraordinarily small polarisability. Furthermore, they usually form a biphasic system with hydrocarbon-type organic solvents at room temperature.[1] The lower layer is the *fluorous* phase, while the upper one is the *organic* phase, having lower density. Such biphasic systems become homogeneous when heated. On cooling, they separate into two liquid phases.

Based on the *like dissolves like principle*, common organic compounds can be made fluorocarbon soluble (*fluorophilic*) if they are substituted with appropriate number and size of fluorous 'pony tails' (e.g. $R_{fn}(CH_2)_x = CF_3(CF_2)_{n-1}(CH_2)_x$, n = 1–10, x =1–3).

The potential of the fluorous phase for chemical processing was fully realized in 1994 when Horváth and Rábai demonstrated that ligands carrying fluorous 'pony tails' (e.g., *fluorous* phosphane $[(R_{f6}CH_2CH_2)_3P]$ and *fluorous* cobalt-phthalocyanine $CoPc(R_{f10})_x$) can carry their co-ordinated metals into the *fluorous* phase with high efficiency when the phases are cooled.[2]

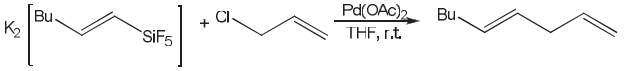
Many innovative catalyst and reagent recovery procedures are based on the *fluorous phase*; thus, many researchers became interested in the design of *phase affinity based* product separations in the early stage of the process development, since the separation of reaction components is controlled by their inherent properties, such as fluorophilicity.[3] As a consequence, reactions that introduce perfluoroalkyl chains into organic molecules became very important. Cross-coupling provides an efficient solution for these requirements.

In the last four decades, transition-metal-catalysed cross-coupling reactions are widely and increasingly used owing to their efficiency and functional group tolerance. Their *fluorous* versions are continuously emerging in the literature. During my PhD work, I was engaged in synthesizing perfluoroalkyl-substituted organosilanes and in studying their reactivity in cross-coupling reactions to provide new and convenient access to *fluorous* styrenes. Since the understanding of the mechanism of a reaction can notably contribute to further optimisation and development, we also aimed at identifying the possible mechanisms involved in our reactions.

Organosilanes in general are highly stable and non-toxic compounds owing to their weakly polarised silicon–carbon bonds, and their final decomposition results in environmentally benign SiO_2. However, they are less reactive toward electrophiles. Due to the

inherent chemical properties of organosilicon compounds, they received smaller attention at the early decades of cross-coupling reaction research.

The first cross-coupling with organosilanes as starting materials was reported by Kumada *et al* (Scheme 1).[4]

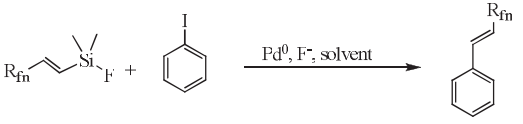


Scheme 1. Kumada coupling

Although this reaction is very interesting theoretically, the need for preparation of the reactive alkenyl pentafluorosilicate dianion species has rendered these protocols less attractive from the point of view of synthetic organic chemists.[5]

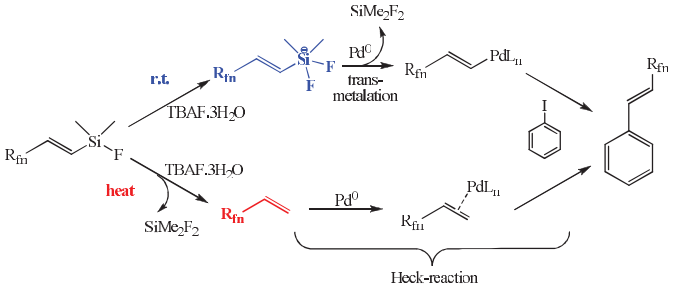
Hiyama *et al.* made a significant step forward by developing a protocol to generate the hypervalent silicate species *in situ* from the tetracoordinated precursor organosilanes.[6,7,8] For the success of this reaction, an activator—most commonly some soluble fluoride source—is essential. Nowadays, Hiyama coupling is applied for industrial-scale syntheses, but perfluoroalkyl-substituted organosilanes have not been tested yet for Hiyama cross-coupling reaction as perfluoroalkyl-alkenyl-group transfer precursors according to our literature search.

At the beginning of my PhD work, we aimed to prepare *fluorous silanes* from commercial perfluoroalkyl iodides and to use them in Hiyama coupling reaction as perfluoroalkyl-ethenyl-group transfer reagents. Their coupling with aryl iodides is expected to provide a new access to fluorous styrenes (Scheme 2).



Scheme 2. Envisioned cross-coupling of the fluorosilanes

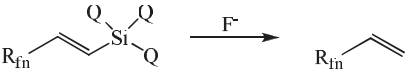
While we were seeking the optimal experimental conditions for the cross-coupling, we observed that the Si–C bond of these alkenylsilanes can be cleaved at higher temperatures with the TBAF activator, and thus the corresponding terminal olefins (R_{fn}–CH=CH_2) are generated *in situ*. These olefins then couple via a Heck-type mechanism with C_6H_5I to afford the same products as if they were reacting via a pure Hiyama-type coupling mechanism (Scheme 3).



Scheme 3. Simplified mechanisms for the formation of ω-perfluoroalkyl-styrenes. Upper path: Hiyama mechanism; lower path: tandem Heck mechanism

Thus, we aimed to study the effect of temperature on the mechanism switching in these coupling reactions and to provide experimental evidences for each path and to explore their scope (Scheme 3).

The fluoride-anion assisted cleavage of perfluoroalkyl-alkenyl fluorosilanes is supposed to be the first step of the above mentioned tandem Heck reactions (Scheme 3). Therefore, as a ramification of our mechanistic considerations, we decided to develop improved procedures for the preparation of perfluoroalkyl-ethenes via protodesilylation of *fluorous organosilanes* and *siloxanes* we used for cross-coupling experiments (Scheme 4).



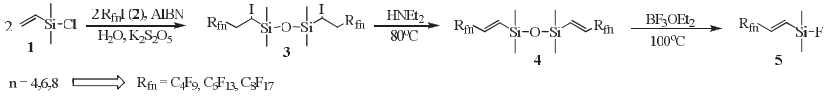
Scheme 4. Protodesilylation of fluorous organosilanes

An important requirement in the design of syntheses is to avoid the formation of by-products that cannot be separated easily. In the above cross-coupling reactions, organosilane by-products $SiMe_2F_2$ and $(SiMe_2F)_2O$ are supposed to be generated by the desilylation of the appropriate olefin precursors, but their separation from the target fluorous styrenes is not troublesome because of their low boiling point. Nevertheless, they can be problematic in other similar reactions. Thus, we initiated the preparation of a novel functionalized silica gel, which is expected to be used as a solid phase supported perfluoroalkyl-ethene precursor.

2. RESULTS

2.1. Preparation of fluorous alkenyl-fluorosilanes

Novel fluorous alkenyl-fluorosilanes (**5a–c**, n = 4, 6, 8) were synthesized in a three-step procedure from commercially available perfluoroalkyl iodides and dimethylvinylchlorosilane.

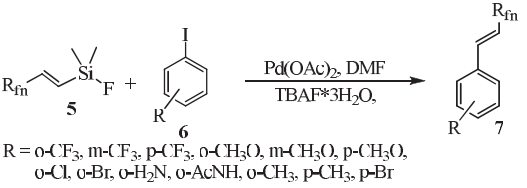


Scheme 5. Easy access to fluorous alkenyl-fluorosilanes (5) in three steps starting from $C_nF_{2n+1}I$

The *in situ* hydrolysis of dimethylvinylchlorosilane (**1**) to tetramethyldivinyl-disiloxane [$(CH_2$=CH–$SiMe_2)O$] was accompanied by the regioselective addition of perfluoroalkyl-iodides (**2**), in the presence of aqueous potassium pyrosulfite, initiated with AIBN, to afford fluorous diiodo-disiloxanes (**3**). The dehydrohalogenation of **3** with $HNEt_2$ resulted in the formation of the appropriate fluorous alkenyl-disiloxanes (**4**). In the following step, disiloxanes **4** are efficiently converted to the appropriate fluorous alkenyl-fluorosilanes (**5**) by heating them with neat borontrifluoride-diethylether complex at a temperature of 100 °C.

2.2. Hiyama couplings at room temperature

The mechanism of the coupling reactions using the above synthesized silanes was found to be of pure Hiyama type, involving fluoride-ion-induced transmetallation without any Heck-type contribution. Synthetic evidences were collected to justify this mechanism (HRMS exact mass measurements on a HPLC-TOF setup; blank and control experiments using perfluoroalkyl ethenes, and protodesilylation). Fluorosilanes **5** were reacted with iodobenzenes **6** at room temperature in Hiyama coupling to afford the appropriate ω-perfluoroalkyl-styrenes **7**.



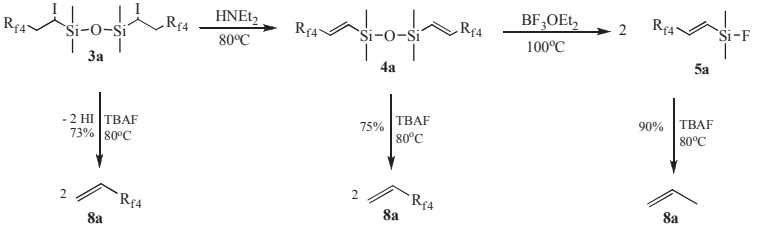
Scheme 6. Coupling reactions with iodobenzenes at room temperature

First, the reaction of fluorosilanes **5a–c** and iodobenzene **6a** was investigated to determine the effect of the length of fluorous chains on product yields. However, no significant

influence of the chain length was observed. Next, we applied substituted iodobenzenes as coupling reagents. The yields increased in the order *ortho-, meta-, para-*, independently of the electronic effect of the substituent. These results may suggest that the reaction of the iodobenzenes is controlled by steric factors.

2.3. The scope of the protodesilylation

Since we found that the coupling reaction of organosilanes in the presence of fluoride anions at elevated temperatures has a *tandem* Heck mechanism, i.e., a protodesilylation step is followed by Heck reaction, we aimed to examine the protodesilylation of silanes **3, 4,** and **5**.



Scheme 7. Protodesilylation of various organosilanes

Silanes **3a, 4a,** and **5a** were tested in a protodesilylation reaction with crystalline tetrabutylammonium fluoride (TBAF*3H_2O) to generate the appropriate perfluoroalkyl-ethene **8a**. It was found that all three organosilanes undergo the protodesilylation. With compound **3**, however, simultaneous dehydrohalogenation takes place. This behaviour is similar to that has been reported by Rábai, Szlávik and co-workers for (β-perfluoroalkyl-α-iodoethyl)-trimethylsilanes ($R_{fn}CH_2CHI–SiMe_3$).[9]

Although TBAF*3H_2O is one of the most commonly used reagent in such reactions, e.g., in the removal of silyl protecting groups, we tried to replace it with more environmentally benign reagents. Our efforts finally resulted in the introduction of the KF/NEt_3/H_2O reagent triad, which eliminated all shortcomings of the usually employed TBAF*3H_2O. As opposed to that compound, our reagent is not expensive and not hygroscopic, and it has more beneficial storage and handling properties.

These experiments revealed that KF/NEt_3/H_2O has the same or better efficiency in protodesilylation reactions than TBAF*3H_2O if at least stoichiometric amount of water was present. It is noteworthy that without water, this reaction does not take place. These experiments explicitly prove that water behaves as a proton source, and the added water does not compromise the nucleophilicity of the fluoride anions supplied by potassium fluoride.

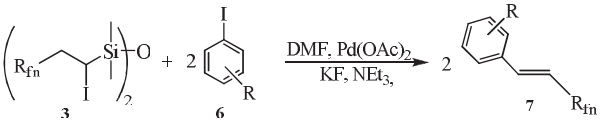
Since all three organosilanes undergo protodesilylation successfully, but β-perfluoroalkyl-α-iodo-siloxanes **3** can be made most easily in one step, we selected them for further coupling studies instead of fluorous alkenyl-disiloxanes **4** and fluorous alkenyl fluorosilanes **5**.

2.4. Virtual Hiyama couplings at elevated temperatures

Our reactivity model involves that the fluoride source cleaves the Si–C bonds in the organosilanes at elevated temperatures, and thus it can generate the appropriate olefins *in situ*. These olefins are then involved in a Heck-type coupling with iodobenzenes to afford the same products as if they were reacted with a pure Hiyama type coupling mechanism. Experimental results (e.g., qualitative data on protodesilylation, on control Heck reactions, and on the effect of the base of the conversion in Pd(0)-catalysed coupling experiments) were collected that support this model.

It was found that β-perfluoroalkyl-α-iodoethyldisiloxanes **3** are the best reagents for this tandem Heck coupling reaction, since they can be prepared most easily from perfluoroalkyl iodides, and they are cleaved to afford the same fluorous olefin **8** as observed with **4** and **5**.

The cleavage of **3** with the KF/NEt_3 pair (and catalytic amount of water) was as effective as with using of TBAF*$3H_2O$.



Scheme 8. Tandem Heck reactions with β-perfluoroalkyl-α-iodoethyldisiloxane

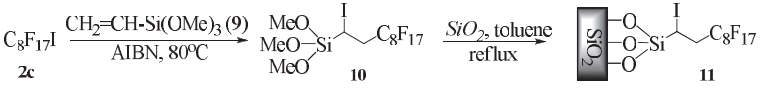
The effect of the substituents of iodobenzenes **6a–i** was tested using **3a** in the presence of KF/NEt_3 and $Pd(OAc)_2$. Styrenes **7a–i** were isolated in good to excellent yields independently from the position of the substituent (*ortho:* -OCH_3, -Cl, -CH_3, *meta*: -OCH_3, -CF_3, *para*: -OCH_3, -CH_3), the electronic effect (EDG: -OCH_3, -CH_3, EWG: -Cl, -CF_3) and the size (-CH_3, -CF_3) of the substituent. Apparently, the reactivity is not influenced by steric or electronic effects this substituent.

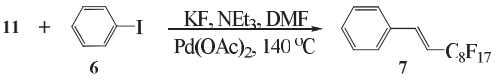
These experiments clearly showed that the cross-coupling of organosilanes may have a temperature-dependent switch of mechanism. Further experiments justified that this phenomenon may also occur in the cross-coupling reactions of classical (i.e. *nonfluorous*) alkenylsilanes.

2.5. Preparation and application of a silica-supported perfluoroalkyl-ethene surrogate

An important requirement in synthesis design is to avoid the formation of by-products. Although separation of styrenes **7a–i** from the low-boiling-point organosilanes generated as by-products ($SiMe_2F_2$, FMe_2Si-O-$SiMe_2F$) was not troublesome, this step might be problematic in other similar reactions affording more volatile target molecules.

We disclosed here the synthesis of a novel functionalized silica gel (**11**), which can be used as a solid-phase-supported perfluoroalkyl-ethene precursor for the tandem Heck reaction.



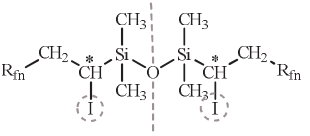


Scheme 9. Tandem Heck reaction with a functionalized fluorous silica gel

The Pd(0)-catalysed tandem cross-coupling reaction of the silica-supported fluorous reagent **11** and iodobenzene was successful with easy product isolation, since no homogeneous by-products are formed.

2.6. NMR spectroscopy

During my PhD work, I elucidated the structure of all new compounds using ^{1}H, ^{13}C, and ^{19}F NMR spectroscopy. Remarkably, the ^{1}H NMR and the ^{13}C NMR spectra at 250MHz of compounds **3** showed some unexpected features as compared to the previously described assignments by Beyou *et al*.[10]



Scheme 10. Structure of compounds 3

Namely, these spectra could not be assigned considering only the chiral centres and the symmetry of the molecule. ^{1}H , ^{13}C and ^{1}H–^{13}C HSQC measurements at 700MHz were performed using compound **3a** to allow better understanding. These results showed that the molecule is not symmetric like compounds **4** and **5**, and this asymmetry is due to the presence of the steric effect of the iodine atom, and also to the chirality of the C_{α} carbons.

2.7. Publications of the author

1. Á. Csapó, A. Bodor, J. Rábai: HIYAMA COUPLING REACTION OF FLUOROUS ALKENYL-FLUOROSILANES: SCOPE AND MECHANISTIC CONSIDERATIONS, *J. Fluorine Chem.* 137 (**2012**) 85-92.
2. Á. Csapó, J. Rábai: SILOXANE BASED SYNTHESES OF FLUOROUS ETHENES AND THEIR TANDEM HECK REACTIONS WITH ARYL IODIDES, *J. Fluorine Chem.* (**2012**). http://dx.doi.org/10.1016/j.jfluchem.2012.07.010
3. Harsányi, É. Dorkó, Á. Csapó, T. Bakó, C. Peltz, J. Rábai: CONVENIENT SYNTHESIS AND ISOLATION OF TRIFLUOROMETHYLTHIO-SUBSTITUTED BUILDING BLOCKS, *J. Fluorine Chem*. 132 (**2011**) 1241-1246.

2.8. Conference posters

1. Á. Csapó, J. Rábai: SYNTHESIS OF FLUOROUS ALKENYL-FLUOROSILANES AND THEIR APPLICATION IN HIYAMA COUPLING REACTION, *16th European Symposium on Fluorine Chemistry*, **2010**, Ljubljana, Slovenia
2. Á. Csapó, J. Rábai: FLUOROS ALKENIL-FLUORSZILÁNOK ELŐÁLLÍTÁSA ÉS ALKALMAZÁSA HIYAMA-KAPCSOLÁSI REAKCIÓBAN, (SYNTHESIS OF FLUOROUS ALKENYL FLUOROSILANES AND THEIR APPLICATION IN HIYAMA COUPLING; in Hungarian), *16th International Conference on Chemistry*, **2010**, Cluj-Napoca, Romania

2.9. Oral presentations

1. Á. Csapó, J. Rábai: THE NATURE OF THE FLUOROUS HIYAMA-REACTION, *1st Indian International Symposium on Fluorine Chemistry,* **2012**, New Delhi, India
2. Á. Csapó, J. Rábai: THE DOUBLE-FACED HIYAMA COUPLING; in Hungarian, *Márton Kajtár Memorial Session,* **2011**, Budapest, Hungary
3. Á. Csapó, J. Rábai: SYNTHESIS AND APPLICATIONS OF FLUOROUS ALKENYL SILANES AND ALKENYL FLUOROSILANES; in Hungarian, *15th International Conference on Chemistry*, **2009,** Tirgu Mures, Romania
4. Á. Csapó, J. Rábai: APPLICATION OF TANDEM HECK REACTION FOR THE INTRODUCTION OF FLUORINE CONTAINING SUBSTITUENTS, in Hungarian*, Heterocyclic Session of the Division of Chemistry, Hungarian Academy of Sciences,* **2011,** Balatonszemes, Hungary.
5. Á. Csapó, A. Bodor, J. Rábai: STRUCTURAL AND MECHANISTIC STUDY OF ALKENYL FLUOROSILANES, in Hungarian, *TÁMOP Conference ELTE*, **2011,** Budapest, Hungary.

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[4] J. I. Yoshida, K. Tamao, M. Takahashi, M. Kumada: STEREOSELECTIVE PREPARATION OF 1,4-DIENES BY PALLADIUM CATALYZED ALLYLATION OF (*E*)-ALKENYLPENTAFLUOROSILICATES. APPLICATION TO TOTAL SYNTHESIS OF (±)-RECIFEIOLIDE, *Tetrahedron Lett*., **1978***, 19*, 2161–2164.

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